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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/988,013 | 11/16/2001 | Shui-on Leung | 18733/1082 | 7681 |

22428 7590 04/04/2006

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| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/988,013 | LEUNG,ET AL. | |
| | Examiner | Art Unit | |
| | David J. Blanchard | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *28--32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-27 are cancelled.

Claim 28 has been amended.

2. Claims 28-32 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

***Rejections Withdrawn***

5. The objection to the abstract because it exceeds 150 words is withdrawn in view of the amended abstract field 2/20/2006.

6. The objections to the specification as lacking the US Patent No. for USSN 08/162,912 and containing typographical errors are withdrawn in view of the amendments to the specification filed 2/20/2006.

7. The rejections of claims 28-32 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "determining residue identities...using computer modeling" and for reciting "A method of designing an amino acid sequence of a variable domain of a humanized monoclonal antibody...obtaining amino acid sequences of the variable domains of the light and heavy chain regions of the resultant humanized monoclonal antibody" are withdrawn in view of the amendments to the claims.

8. The rejection of claims 28-32 under 35 U.S.C 103(a) as being unpatentable over Queen et al (WO 90/07861) in view of Adair et al (US Patent 5,859,205) is withdrawn in

view of applicant's arguments and the amendments to the claims which require both variable domains of the humanized antibody have framework regions selected from two or more human variable domains.

***Response to Arguments***

9. The rejection of claims 28-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for introducing new matter into the claims is maintained.

The response filed 2/20/2006 again points to paragraphs [0043]-[0046], [0048], [0053] and [0067] of the as filed specification for support of claims 28-32. The response also states that for purposes of 35 U.S.C. 112, first paragraph, Applicants need not be in possession of every possible species of humanized antibody encompassed within the genus of the claimed method and while a certain amount of experimentation might be required to determine the sequences to design a humanized monoclonal antibody, the method of determining, selecting, incorporating, retaining and finally obtaining the desired amino acid sequences in the design of humanized monoclonal antibodies are described in detail in the specification. Further, Applicant states that the various steps recited in the claims are well known in the art and a matter of routine experimentation for those skilled in the art. This has been fully considered but is not found persuasive. The examiner acknowledges that Applicant's need not be in possession of every possible species of humanized antibodies encompassed within the genus of the claimed method, however, the written description must convey to one skilled in the art that the

inventors at the time the application was filed had possession of the claimed invention. Further, Applicant's arguments regarding the amount of guidance and direction provided in the specification and the assertion that the various method steps in the claims are well known in the art and a matter of routine experimentation appear to go more towards enablement, i.e., how to make and use, rather than the disputed issue of new matter for lack of adequate written support. The issue is not whether one skilled in the art could make and use the claimed method based on the guidance provided in the specification or whether practicing the claimed method is merely a matter of routine experimentation, but rather the issue is whether the as filed disclosure provides adequate written support for the presently claimed invention. The written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). See MPEP 2161.

Applicant asserts that the examiner is incorrect in interpreting that the range of 75 to 92.3% only applies to the light chain framework regions and applicant argues that paragraph [0043] immediately following the residue identity range 75 to 92.3% begins a new sentence with "similarly", which clearly indicates that the range of sequence identities also applies to the heavy chain. Applicant concludes that there is adequate written support for the human framework regions that have approximately 75 to 92.3% sequence identity with the framework regions in the monoclonal antibody to be humanized. This has been fully considered but is not found persuasive. As presented

the claims are drawn to a method of humanizing a monoclonal antibody wherein the method comprises selecting framework regions from variable domains of two or more human monoclonal antibodies wherein each framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework region in the monoclonal antibody to be humanized and wherein at least three of said selected framework regions are from different human monoclonal antibodies. The as filed disclosure does not provide adequate written support for the presently claimed method in which human framework regions are selected from two or more human monoclonal antibodies wherein each human framework region has a sequence identity of approximately 75 to 92.3% to the corresponding framework region in the monoclonal antibody to be humanized. It is reiterated that paragraph [0043] discloses the amino acid sequence identity of 75 to 92.3% in the context of facilitating the computer modeling of the variable domains of the heavy and light chains for identifying framework residues that potentially have critical interactions with the CDRs and should be retained in the humanized antibody. There is no disclosure at paragraph [0043] for selecting framework regions from two or more human monoclonal antibodies wherein each framework region has a sequence identity of approximately 75 to 92.3%. Further, while paragraph [0067] discloses the selection of the human frameworks exhibiting the highest degree of sequence homology to the frameworks of the Vk and VH domains of the LL2 antibody, there is no disclosure or contemplation that the criteria for selecting human framework regions requires that they be approximately 75 to 92.3% identical to the corresponding framework regions in the monoclonal antibody to be humanized. Where is it disclosed

or even contemplated that the claimed humanization method selects framework regions from two or more human monoclonal antibodies or wherein at least three of said human framework regions are from different human monoclonal antibodies? As written, the claims encompass a method of antibody humanization wherein the human framework regions are individually selected from variable domains of different human monoclonal antibodies, i.e., wherein all four framework regions, FR1, FR2, FR3 and FR4 are from different human monoclonal antibody variable domains, which is not clearly disclosed and adequately supported in the as filed disclosure. Additionally, the disclosure at paragraph [0067] selects the most homologous framework sequences from human antibodies in the kabat database, however, the claims recite that the human antibodies are "human monoclonal antibodies". There is insufficient written support for "human monoclonal antibodies". Furthermore, even considering the selected framework regions at paragraph [0067], the human REI framework region was selected for the light chain and the human EU framework region was selected for the heavy chain with the exception that human NEWM was selected for framework region 4 (FR4). Thus, the sequence identity between the murine LL2 framework regions and the selected human framework regions of the light chain are 69% for FR1, 72% for FR3 and 72% for FR4 (Figure 1 and legend) and the selected human framework regions of the heavy chain are 73%, 71% and 62.5% for FR1-3, respectively. Thus, the disclosure of selecting a human light chain framework region from one human variable domain (i.e., REI) wherein three of the four framework regions have less than 75% sequence identity to the corresponding framework region of the monoclonal antibody to be humanized (i.e.,

LL2) would not have led the skilled artisan to the broader limitations of selecting human framework regions from variable domains of two or more human monoclonal antibodies wherein each framework region has 75 to 92.3% sequence identity with the corresponding framework region of the monoclonal antibody to be humanized as presently claimed. Further, the selection of the NEWM for FR4 of the heavy chain was due to the lack of X-ray coordinate data for the EU sequence (see paragraph [0043], lines 11-16). Similar to the light chain variable domain, the disclosure of selecting a human heavy chain framework regions from two human variable domains of two or more human monoclonal antibodies (i.e., EU and NEWM) wherein three of the four framework regions have less than 75% sequence identity to the corresponding framework region of the monoclonal antibody to be humanized (i.e., LL2) would not have led the skilled artisan to the broader limitations of selecting human framework regions from variable domains of two or more human monoclonal antibodies wherein each framework region has 75 to 92.3% sequence identity with the corresponding framework region of the monoclonal antibody to be humanized heavy or wherein at least three of the selected framework regions are from different monoclonal antibodies. One of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus of the claimed method in view of the species disclosed.

For these reasons the rejection of claims 28-32 under 35 U.S.C 112, first paragraph as introducing new matter is maintained.

***New Grounds of Objections/Rejections***

10. The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text. See MPEP 608.01(b).

11. Claims 28-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because the preamble of claim 28 recites a method of designing amino acid sequences of variable domains of a humanized antibody, whereas step (a) only determines the residue identities between amino acid sequences of a variable domain of a monoclonal antibody and corresponding variable domains of two or more human monoclonal antibodies. Are both heavy and light chain variable domains of a monoclonal antibody humanized by comparing only the heavy chain variable domain (i.e., "a variable domain") of a monoclonal antibody to be humanized to the heavy chain variable domains of two or more human monoclonal antibodies or by comparing only the light chain variable domain of a monoclonal antibody to be humanized to the heavy chain variable domains of two or more human monoclonal antibodies?

***Conclusions***

12. No claim is allowed.

13. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER